Docket No. UF-243X

DECLARATION (37 CFR 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name; and

I believe that I am the original, first, and sole inventor (if only one name is listed below), or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **MATERIALS AND METHODS FOR INHIBITION OF IgE PRODUCTION** the specification for which

☐ is attached hereto.

☒ was filed August 25, 2000, Serial No. 09/648,864.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code §119 and/or §365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application Serial No.	Country	Filing Date	Priority Claimed

I hereby claim priority benefits under Title 35, United States Code §119 of any provisional application(s) for patent listed below:

Application Serial No.	Filing Date	Priority Claimed
60/151,026	August 27, 1999	Yes

I hereby claim the benefit under Title 35, United States Code, §120 and/or §365 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following persons registered to practice before the Patent and Trademark Office as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith: David R. Saliwanchik, Reg. No. 31,794; Jeff Lloyd, Reg. No. 35,589; Doran R. Pace, Reg. No. 38.261; Christine Q. McLeod, Reg. No. 36,213; Jay M. Sanders, Reg. No. 39,355; James S. Parker, Reg. No. 40,119; Jean Kyle, Reg. No. 36,987; Frank C. Eisenschenk, Reg. No. 45,332; Seth M. Blum, Reg. No. 45,489; Glenn P. Ladwig, Reg. No. 46,853.

I request that all correspondence be sent to:

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Signature of Third Joint Inventor

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Name of Fourth Joint Inventor _____

Residence _____ Citizenship _____

Post Office Address _____

_____

_____ Date _____

Signature of Fourth Joint Inventor

Patent Application
Docket No. UF-243X
Serial No. 09/648,864

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Janet L. Andres, Ph.D.
Art Unit	:	1646
Applicants	:	Howard M. Johnson, Mustafa G. Mujtaba
Serial No.	:	09/648,864
Filed	:	August 25, 2000
Conf. No.	:	6790
For	:	Materials and Methods for Inhibition of IgE Production

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HOWARD M. JOHNSON, Ph.D. UNDER 37 CFR §1.132

Sir:

I, Howard M. Johnson, Ph.D., hereby declare:

THAT, I am a co-inventor of the subject matter claimed in U.S. patent application Serial No. 09/648,864 (hereinafter the '864 application);

THAT, I have read and understood the '864 application;

THAT, I have read and understood the rejection of claims in the Office Actions mailed January 28, 2002, October 21, 2002, and May 19, 2003 in the '864 application;

AND, being thus duly qualified, do further declare:

The claims of the subject application are rejected under 35 USC §103(a) as obvious over the publications by Pene *et al.* (1988), Gruschwitz *et al.* (1993), or Kimata *et al.* (1995), and further in view of Johnson *et al.* (WO 97/39127). The Examiner asserts that the cited primary references teach the use of interferon alpha to downregulate IgE production. While acknowledging that the primary references do not teach that interferon tau can downregulate IgE production, the Examiner asserts that it would have been obvious to substitute interferon tau for interferon alpha in view of the Johnson *et al.* reference which, according to the Examiner, teaches that interferon alpha and interferon tau bind to the type I receptor and have similar

biological activities. From this, the Examiner concludes that the ordinarily skilled artisan, at the time of the subject invention, would have expected that interferon tau, like interferon alpha, would also downregulate IgE production.

I respectfully assert that type I interferons do not share all of the same biological activities and that an ordinarily skilled artisan, at the time of our invention, would not have reasonably expected that interferon tau would downregulate IgE production. One of the primary distinctions between interferon tau and other type I interferons is that there is a significant difference in the toxicity associated with interferon tau versus other interferons. Interferon tau is substantially less toxic to eukaryotic cells than interferon alpha. In my opinion, this is a qualitative difference between interferon tau and the other interferons.

There are other qualitative differences between interferon tau and other type I interferons, such as apoptosis inducing activity. In my laboratory, interferon tau was compared with human interferon alpha 2A for induction of apoptosis on the human Daudi cell line (Subramaniam *et al.*, 1998, "Type I interferon induction of the Cdk-inhibitor $p21^{WAF1}$ is accompanied by ordered G1 arrest, differentiation and apoptosis of the Daudi B-cell line" *Oncogene*, Vol. 16, pp. 1885-1890). As shown in Figure 4 of the Subramaniam *et al.* publication, Daudi cells treated with interferon tau exhibited normal morphology, similar to that of untreated control cells. In contrast, exposure of Daudi cells to interferon alpha 2A, at 10-fold less concentration, produced classic morphologic changes characteristic of cellular apoptosis (McConkey *et al.*, 1996, "Signal Transduction Pathways in Apoptosis" *Stem Cells*, Vol. 14, pp. 619-631). These changes consist of membrane blebing and nuclear fragmentation that is indicative of chromosome disruption. These results show that interferon tau does not induce cellular apoptosis under conditions where interferon alpha does induce apoptosis in a human cell line. The above described apoptosis inducing activity is an example of another qualitative, functional distinction between interferon tau and other type I interferons.

In a recent study, it was shown that interferon tau promotes a T-helper 2 (Th2) bias in suppression of autoimmune encephalomyelitis in a mouse model of multiple sclerosis (MS) (Soos *et al.*, 2002). Specifically, it was shown that oral administration of interferons alpha, beta and tau to myelin basic protein-specific T-cell receptor transgenic mice promoted secretion of

the Th2 cytokine interleukin-10 with similar efficiency. Unexpectedly, however, interferons alpha and beta also induced secretion of the T-helper 1 (Th1) cytokine interferon gamma, whereas interferon tau did not induce secretion of interferon gamma. Activation of Th1 cells, with the subsequent production of interferon gamma, can result in proinflammatory responses, which may explain some of the undesirable side effects of interferon beta treatment of multiple sclerosis. Interferon tau does not activate the Th1 arm of the T-cell system. These differences between interferons alpha, beta and tau could not have been predicted based on simple reference to receptor specificity.

Similar to interferon gamma, type I interferons have been shown to possess STAT-independent functions (Gongora *et al.*, 2000). Specifically, it has been shown that inhibition of interleukin-7-dependent B lymphopoiesis by interferon alpha or beta is unaffected in STAT-1-deficient mice. The data indicate that type I interferons can activate an alternative signaling pathway in which STAT1 is not an essential component. Although interferons are classified into groups or types, they possess aspects of unique structure such as their differences in amino acid composition. These differences could play a role in the non-STAT transcription factor function of these individual type I interferons. In particular, interferon tau contains more amino acid residues than do alpha interferons, as well as more differences in the sequence when compared to alpha interferons as a group (Bazer and Johnson, 1991). Even among alpha interferons, there are unpredictable differences in function. It has been shown recently, for example, that five subtypes of human alpha interferons exhibited different anticellular activity against chronic myelogenous leukemia cells (Yanai *et al.*, 2002). The authors state that "these data indicate in vitro distinctions between IFN-α subtypes that should be appreciated more in the clinic." (emphasis added)

Thus, while interferons tau and alpha (and other type I interferons) may have some similar biological activities, they also exhibit significant differences in activities. Accordingly, I respectfully submit that an ordinarily skilled artisan, at the time of our invention, could have only speculated that interferon tau would downregulate IgE production.

Accordingly, I respectfully maintain, based on my numerous years of involvement in interferon research and on the evidence presented herein, that the invention claimed in the '864 application is not obvious over the cited references.

A copy of each publication cited herein is attached to this Declaration.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: Howard M. Johnson

Howard M. Johnson, Ph.D.

Date: August 29, 2003